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Disturbances of visual motion perception in bipolar disorder

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Abstract

Objectives—While cognitive deficits have been well-documented in patients with bipolar disorder, visual perception has been less well-characterized. Such deficits appear in schizophrenia, which shares genetic risk factors with bipolar disorder, and may contribute to disturbances in visual cognition and learning.

Methods—The present study investigated visual perception in bipolar disorder using psychophysical tests of contrast sensitivity, dot motion discrimination, and form discrimination. The relationship of these measures to mood state, medication status, and cognitive function was investigated. Sixty-one patients with type I bipolar disorder and sixty-seven comparison subjects were tested.

Results—Results indicated a deficit in dot motion trajectory discrimination in both euthymic and ill individuals with bipolar disorder, as well as a global deficit in moving grating contrast sensitivity. Ill individuals with bipolar disorder were impaired in psychomotor processing, but this finding was not related to visual processing performance.

Conclusions—These findings could be due to disturbances in specific visual pathways involved in the processing of motion properties, or to a more general deficit which impairs processing of temporally modulated stimuli.

Keywords

bipolar disorder; magnocellular; motion; parvocellular; psychiatric disorders; temporal processing; vision

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Bipolar disorder (BPD) is a psychiatric disorder characterized by periods of mania or hypomania. Depressive episodes typically occur as well, and many patients also demonstrate psychotic features. While marked alterations in mood are central to the diagnosis of BPD, cognitive function is also affected by the illness. Tests of attention, executive function, and psychomotor speed are impaired in patients with BPD in the depressed or manic state. Moreover, less severe cognitive deficits are also apparent in the euthymic state, which affect sustained attention, working memory, verbal and spatial learning, planning, and psychomotor speed (1-3). Sensory and perceptual processes have been less well characterized in BPD. Marked disturbances in visual perception have been identified in schizophrenia (4-8). Since schizophrenia may share common genetic risk factors with BPD (9), early stage vision may be affected in BPD as well. Such deficits would indicate that the pathophysiology of BPD may affect sensory pathways and contribute to deficits in visual cognition.

Several lines of evidence indicate that visual perception may be perturbed in BPD. Chen et al. (5) reported deficits on a velocity discrimination task that differentiated patients with BPD and those with schizophrenia. Patients with BPD showed deficits in velocity discrimination only at high velocities, while patients with schizophrenia showed deficits for low, intermediate and high velocities. Chen et al. argued that these findings indicated patients with schizophrenia showed a motion processing deficit that is dependent on velocity cues, while patients with BPD, on the other hand, showed a disturbance of temporal processing that is not specific to motion processing. Patients with BPD have been reported to show deficits in visual backward masking performance similar to those of schizophrenia and schizoaffective disorder, suggestive of disturbances in sensory processing [(10); see (11) for a review]. Green et al. (12) observed that patients with BPD in the manic phase showed backward masking deficits, and that these deficits could be due to transient channel abnormalities (13). Perris (14) reported lower flicker fusion frequencies in BPD, also consistent with disturbances in temporal processing at higher modulation frequencies. Deficits in visual motion perception or temporal processing could also contribute to abnormal pursuit eye movements, which have been reported in patients with BPD compared to control subjects, and in the relatives of patients with affective disorders (15-20). The effect of mood state was addressed in a study by Keri et al. (21). Using a Vernier threshold task, Keri et al. found that patients with BPD in the depressed state were impaired for both magnocellular (M) and parvocellular (P) biased conditions, but after remission the deficits were no longer significant. In summary, deficits in visual processing thought to represent information flow from the thalamus to different levels of cortical processing may be a common feature in BPD, and may be more severe for transient, moving or temporally modulated stimuli. These findings implicate disturbances in visual perception in BPD which may vary with symptom severity or clinical state.

Visual pathways have been described on the basis of response properties to the M and P neurons of the lateral geniculate nucleus (22, 23). These neurophysiological studies have indicated the M pathway is characterized by high contrast sensitivity, high temporal resolution, low spatial resolution, and insensitivity to color. The P pathway, on the other hand, is characterized by low contrast sensitivity, low temporal resolution, high spatial resolution, and response to color. The M pathway has response properties similar to the

transient channel defined by psychophysical studies, and the P pathway is similar to the sustained channel. These pathways are also linked to functionally differentiated cortical streams. The M pathway primarily projects to the dorsal occipito-parietal stream, which is associated with spatial localization, motion perception and motor planning. The P pathway is biased toward the ventral occipital-inferior temporal stream associated with object recognition (24-26). Nevertheless, cross-talk occurs between pathways, beginning in V1, where P and M projections from the thalamus are distributed across layers to facilitate different computational functions. Many perceptual tasks, such as extracting object properties from motion cues, rely on integration of signals from the P and M neurons of the LGN. Within the cortical pathways, signaling is bidirectional, so that top down modulation of perceptual processing is pervasive (27). Previous findings suggest that functions subserved by the M or dorsal pathways may be more affected in BPD (12, 13). In the current study, psychophysical tests were used to probe the integrity of these visual pathways.

Visual psychophysics utilizes visual tasks in which variables such as contrast, velocity, duration or degradation of the stimulus are manipulated in order to determine thresholds for detection of visual features, such as motion or spatial frequency. Testing can be designed to probe M or transient pathway function by presenting stimuli with low luminance contrast, low spatial frequency and high temporal frequency properties. Conversely, the P or sustained pathway can be behaviorally probed by testing thresholds to static, high spatial frequency stimuli. Motion and form coherence tasks can be used to test functions associated with the dorsal and ventral cortical pathways, respectively. Since similar paradigms have been used in schizophrenia, this approach may identify processes that are affected similarly by the two disorders, as well as processes that differentiate them.

The aim of the present study was to determine whether visual processing is affected in BPD, and to investigate whether these deficits are associated with mood state, medication status, demographic variables or neuropsychological function. In order to assess visual processing, tests of contrast sensitivity were designed to assess the M and P pathways, and dot motion and form coherence tests were designed to evaluate the dorsal and ventral cortical pathways. The dependent variable was the psychophysical threshold for each task, which allowed matching of task difficulty across related conditions (28, 29). We also evaluated the mood state of patients with BPD at the time of testing to determine whether our findings differed between the euthymic and manic/depressed mood states. We initially hypothesized that the BPD group would show deficits in M pathway, and subsequently dorsal cortical pathway visual processing, similar to the findings reported in the literature in patients with schizophrenia. We also evaluated participants with BPD on measures of intellectual performance, focusing on measures that have been found to be impaired in individuals with BPD. These measures were compared to healthy control (HC) participants to determine whether subjects with BPD were impaired intellectually, and whether measures of general intellectual function were correlated with visual perception. Neuropsychological functioning has been correlated with performance on several psychophysical tasks in schizophrenia (7, 30), and Javitt (31) has argued that bottom-up deficits in cognitive processing are driven in part by perceptual deficits in schizophrenia. We hypothesized that correlational analyses between visual processing tasks and neuropsychological performance in BPD would reveal similar relationships. More specifically, we hypothesized that perceptual performance would

influence neuropsychological tasks that tap visual cognition in those with BPD. Finally, to determine whether medication affected performance, we compared those that were not taking medication at the time of testing to those taking medication.

Materials and methods

Subjects

The study included a group of patients with BPD and a group of HC subjects with no history of psychiatric disorder. Sixty-one subjects (40 women, 21 men) with BPD and 67 HC subjects (35 women, 32 men) participated. The mean age of subjects was 39 years for the HC group and 40 years for the BPD group [$t(125) = -0.841$, $p = 0.402$]. All participants had completed at least grade-school level education. We did not measure visual acuity in 16 subjects, but the remaining participants had Snellen visual acuity of 20/40 or better. Exclusion criteria was: (i) any history of neurological disease, (ii) history of head injury that resulted in loss of consciousness > 5 minutes, (iii) a current or previous diagnosis of substance or alcohol dependence, or (iv) alcohol or substance use within 24 hours prior to testing. Table 1 provides the group characteristics. Written and oral informed consent was obtained from all subjects. Patients with BPD were evaluated using the Structured Clinical Interview for DSM-IV (SCID) Axis I disorders (SCID-I) (32) and clinical records to obtain a DSM-IV diagnosis. HC participants did not meet DSM-IV criteria for a diagnosis of psychosis or BPD based on the SCID–non patient interview. The SCID-II modules for schizoid, paranoid, and schizotypal personality disorders (33) were also administered in order to exclude participants presenting with these personality disorders from the control group.

Diagnostic assessment and clinical measures

Tests from the Wechsler Adult Intelligence Scale-III (WAIS-III), i.e., Similarities, Picture Completion, Digit Span, and Digit Symbol were used to assess dimensions of current intellectual function in verbal comprehension (*Similarities*), perceptual organization (*Picture Completion*), verbal working memory/focused attention (*Digit Span*), and psychomotor performance (*Digit Symbol*) (34, 35). Age-scaled scores were used for all statistical analyses. The Young Mania Rating Scale (YMRS) (36) and structured interview for the Montgomery–Åsberg Depression Rating Scale (MADRS) (37) were given to participants with BPD at time of testing to determine mood state. The following numerical criteria were used to classify patients by categorical mood state: mania: YMRS > 19 ; hypomania: YMRS > 11 (but less than 20); and depression: MADRS > 19 (38, 39). Within the BPD group, 29 were euthymic at the time of testing, and 32 were experiencing a BPD episode [depressed ($n = 6$), manic ($n = 14$), hypomanic ($n = 7$), and mixed ($n = 5$)].

Form and motion noise thresholds

Perception of form and dot motion properties were evaluated using psychophysical tests [see Fig. 1 for detailed methods; see (7, 29)]. Fifty-five subjects with BPD and 60 HC participants were tested. In the form discrimination task, subjects were required to discriminate between two shapes (circle versus square with rounded corners) at different levels of static noise. The stimuli subtended 2.9° of visual angle and were presented for three

seconds, with a viewing distance of 70 cm. The subject responded with a key press to indicate which stimulus was presented. The dot motion trajectory discrimination task consisted of a field of moving dots moving either right or left across the screen at an apparent velocity of $3.5^\circ/\text{sec}$. A total of 100 dots were presented for 500 msec in a rectangular display subtending 8.1° visual angle with a viewing distance of 70 cm. The percentage of dots moving in random trajectories was varied to obtain thresholds. The subject responded verbally to indicate the direction of the coherent dot motion, and the experimenter entered the response to initiate the next trial. Both tasks used an adaptive staircase method to estimate performance thresholds (40). If the subject was correct on two successive trials, noise was added to the stimulus. This made the next judgment more difficult. If the subject was incorrect, noise was removed from the stimulus. Noise was first introduced in increments of 10%, then after the first error, in increments of 5%. After the fourth error, the increments were reduced to 2%. The subject's performance gradually converged around a threshold value, which was the amount of coherence (signal) required to obtain a 70.7% performance level. The coherence threshold, calculated as the mean value of the final six trials of the staircase (7, 29), was the dependent measure used for analysis. Motion discrimination coherence thresholds were subtracted from 100 to indicate the amount of noise obscuring the direction of motion. For both the form and motion discrimination tasks higher values indicated better performance (i.e., more tolerance for noise).

Contrast sensitivity tests

Contrast sensitivity for gratings was tested for both static and moving spatial frequency gratings. Sinusoidally modulated, vertically oriented gratings were presented as stimuli using the Morphonome Image Psychophysics System (41) on a PowerMac computer platform with a luminance calibrated CRT monitor. Gratings were spatially modulated with a Gaussian envelope subtending 8.37° of visual angle at a viewing distance of 115 cm. Two types of tasks were used. A grating detection task with a static, high spatial frequency grating was used to probe the P pathway. A low spatial frequency grating which was temporally modulated to produce apparent motion was used to probe the M pathway. In the static grating detection task, a grating with a spatial frequency of 9.9 cycles/degree of visual angle was used as the target. The grating was initially presented for 1000 ms at 42% Michelson contrast. Tone pips signaled the onset and offset of the trial. Fifty percent of the trials presented a grating and 50% were null trials. The subject responded verbally regarding whether a grating was present or not, and the experimenter entered the response and initiated the next trial. Fifty-five subjects with BPD and 64 HC subjects were tested on the static grating test. In the moving grating discrimination task, a sinusoidal grating with a spatial frequency of 1.3 cycles/degree was modulated to produce apparent motion at one of three temporal frequencies (2.1, 9.3, and 18.8 cycles/sec) for 480 msec. The grating was initially presented at 30% Michelson contrast. On each trial, the subject indicated whether the grating appeared to move to the right or to the left. For both the static and moving grating tasks, a staircase method was used to estimate contrast thresholds (41, 42). Contrast was varied in steps of 0.05 log units. The staircase procedure varied contrast based on correct and incorrect responses, increasing the contrast by three steps (0.15 log units) for each incorrect response and decreasing by one step for each correct response. At asymptote, this procedure

provides a 75% correct threshold level, which is calculated on the moving average of the last 16 trials in a sequence, arriving at the threshold estimate when the standard deviation and least squares slope of the step values reach a stable criterion ($SD < 0.3\%$, $slope < 0.1\%$). This procedure converges rapidly to a stable threshold estimate in about 25 trials. For all tasks, \log_{10} contrast sensitivity ($1/contrast$) was used for statistical analysis. Higher contrast sensitivity values indicated better performance. Forty-three subjects with BPD and 58 HC subjects were tested on the moving gratings task.

Statistical analysis

Analysis of variance (ANOVA) was used to evaluate effects of Groups, Tasks, and interactions among these factors. First, a two-group ANOVA was used (HC versus BPD), to test for overall differences between groups. If group differences were significant, a three-group ANOVA was used (HC, euthymic BPD, and ill BPD) to further investigate effect of mood state on performance. *T*-tests were used to evaluate interactions. Similar procedures were used to evaluate the number of trials required to reach threshold between groups. Linear regression analyses were conducted to evaluate the relationship between neuropsychological and visual task performance across groups. Diagnosis was entered in the first block, with scaled scores for Picture Completion, Digit Symbol Coding, Similarities, and Digit Span entered in the second block, each using the *Enter* method. Pearson correlation coefficients were used to test for relationships between neuropsychological and visual task performance for each diagnostic group separately. A *p*-value of < 0.05 was used for significance testing and Bonferroni corrected values were reported for post hoc tests. With respect to missing data, seven subjects did not complete the neuropsychological tests, five did not complete the form discrimination task, thirteen did not complete the dot motion task, nine did not complete the static contrast sensitivity task, and twenty seven subjects did not complete all three moving contrast sensitivity tasks. Missing data was generally equivalent across diagnostic groups, and subjects with missing data were not used in relevant analyses.

Results

Form and dot motion discrimination

For the dot motion discrimination task (Table 2), one-way ANOVA (HC: $n = 60$, BPD: $n = 55$) revealed a main effect of Group [$F(1,114) = 14.79$, $p = 0.001$], indicating subjects with BPD performed worse than HC subjects on this task. One-way ANOVA evaluating mood state (euthymic: $n = 27$, ill: $n = 28$) also revealed a main effect of Group [$F(2,114) = 7.33$, $p = 0.001$]. Post-hoc analyses revealed that both euthymic (Bonferroni, $p = 0.007$) and ill (Bonferroni, $p = 0.007$) patients were impaired. Patients did not differ in their performance based on their mood state (euthymic versus in a BPD episode; Bonferroni, $p = 1.00$).

For the form discrimination task (HC: $n = 62$, BPD: $n = 61$), one-way ANOVA revealed no significant differences between HC subjects and patients with BPD [$F(1,122) = 0.112$, $p = 0.739$].

Contrast sensitivity for gratings

Repeated measures ANOVA on \log_{10} contrast sensitivity with the factors of Test (3: 2.1 Hz, 9.3 Hz, and 18.7 Hz) and Group (HC: $n = 58$, BPD: $n = 43$) revealed a nearly significant main effect of Group [$F(1,99) = 3.80$, $p = 0.054$] (Table 3), indicating that participants with BPD had lower sensitivity overall than HC participants. There was also a main effect of Test [$F(2,198) = 434$, $p < 0.001$] indicating that sensitivity on this task significantly decreased as temporal frequency increased (mean difference 2.1 c/d – 9.3 c/d: 0.068; mean difference 9.3 c/d – 18.7 c/d: 0.536) (least significant difference, $p < 0.001$). The Group \times Test interaction was not significant. A separate repeated measures ANOVA investigating effects of mood state (euthymic: $n = 20$, ill: $n = 23$) did not show a significant main effect of Group [$F(2,98) = 2.30$, $p = 0.106$], although pairwise comparisons showed that HC participants had significantly higher sensitivity compared to euthymic participants with BPD ($p = 0.040$). Sensitivity for ill participants with BPD did not differ significantly from either the HC participants or euthymic patients with BPD ($p = 0.287$, $p = 0.370$, respectively). There remained a main effect of Test [$F(2,196) = 355$, $p < 0.001$], indicating significantly decreased sensitivity with each increase in temporal frequency (pairwise comparisons all $p < 0.001$). There were no Group \times Test interactions. Repeated measures ANOVA on the number of trials required to reach threshold for each Test (2.1 Hz, 9.3 Hz, and 18.7 Hz) and Group (HC, BPD) revealed a significant main effect of Test [$F(2,190) = 78.41$, $p < 0.001$] indicating significantly fewer number of trials required to reach threshold as motion increased (2.1 Hz: mean = 44.62, 9.3 Hz: mean = 40.45, 18.7 Hz: mean = 34.22; all $p < 0.001$). The Test \times Group interaction was not significant ($p = 0.483$), indicating that both groups required a similar number of trials to reach threshold on each test.

One-way ANOVA on \log_{10} contrast sensitivity values for the static grating paradigm revealed no significant differences between groups (HC: $n = 64$, BPD: $n = 55$) [$F(1,118) = 0.231$, $p = 0.632$]. A one-way ANOVA on the number of trials required to reach threshold on the static grating task revealed no significant differences between groups [$F(1,120) = 0.624$, $p = 0.431$].

Neuropsychological tests

One-way ANOVA revealed a significant difference between HC subjects ($n = 63$) and patients with BPD ($n = 59$) for the Digit Symbol task [$F(1,121) = 14.16$, $p < 0.001$], with subjects with BPD performing more poorly than HC participants. ANOVA investigating mood state (euthymic: $n = 28$, ill: $n = 31$) also revealed a main effect of Group [$F(2,121) = 10.76$, $p < 0.001$]. Post-hoc tests indicated that HC participants performed significantly better on this task than participants with BPD who were ill (Bonferroni, $p < 0.001$), but did not differ in performance from euthymic patients with BPD (Bonferroni, $p = 0.399$). Furthermore, euthymic patients with BPD performed significantly better than individuals with BPD experiencing a mood episode (Bonferroni, $p = 0.033$).

One-way ANOVA also revealed a trend for a decrement in performance in BPD on the Digit Span task [$F(1,121) = 3.77$, $p = 0.055$]. Similar to the Digit Symbol findings, ANOVA investigating mood state (euthymic: $n = 28$, ill: $n = 31$) also revealed a main effect of Group [$F(2,121) = 3.60$, $p = 0.030$]. Post-hoc tests once again indicated that participants with BPD

who were currently ill were impaired compared to HC subjects (Bonferroni, $p = 0.027$), while euthymic patients did not differ from the HC group (Bonferroni, $p = 1.00$). There were no significant differences between groups for the Picture Completion or Similarities.

With respect to measures of neuropsychological performance, linear regression analyses revealed that Picture Completion significantly predicted motion discrimination performance across groups, beyond that significantly predicted by Diagnosis (Table 5) and was significantly correlated for each group separately (Table 6). Positive β and correlation coefficients indicated that dot motion trajectory identification improved with better Picture Completion performance. Dot motion discrimination performance was also correlated with Similarities for the BPD group only (Table 6), indicating that dot motion trajectory identification improved with better Similarities performance only in BPD.

Linear regression analyses for form discrimination did not reveal a significant diagnostic or neuropsychological predictor, however, performance on the form discrimination task for subjects with BPD was correlated with Similarities (see Table 6), indicating that identification of forms improved with better Similarities performance for the BPD group.

Linear regression analyses for static contrast sensitivity across groups did not reveal a significant diagnostic or neuropsychological predictor, however, performance on the static contrast sensitivity task for patients with BPD was correlated with Picture Completion, Similarities, and Digit Span, indicating that improved static contrast sensitivity was associated with better neuropsychological performance on these tasks for the BPD group only.

Linear regression analyses revealed that Digit Symbol significantly predicted 2.1 Hz moving contrast sensitivity (Table 5) across groups, but in correlation analyses for each group separately this correlation was only found for the HC group (Table 6). While linear regression did not reveal a significant predictor of 9.3 Hz moving contrast sensitivity, correlation analyses revealed a significant positive correlation between 9.3 Hz contrast sensitivity and Digit Symbol for the HC participants only. Finally, linear regression indicated that Digit Symbol was a significant predictor of 18.7 Hz contrast sensitivity performance (Table 5) across groups, however, correlation analyses indicated that this positive relationship was only found for the HC group (Table 6).

Correlations between clinical measures and visual performance in BPD

The YMRS scale correlated negatively with static contrast sensitivity (Table 4) among subjects with BPD, indicating that the more manic symptoms a participant exhibited at the time of testing, the worse their static contrast sensitivity performance. There were no significant correlations between YMRS/MADRS scales and form or motion discrimination performance.

Medication and performance in BPD

Twelve of the participants with BPD were not taking medication at the time of testing. These patients were compared to subjects with BPD who were receiving medication for their BPD to determine if differences in performance on the visual processing could be related to

medication status. There were no differences between medicated and nonmedicated participants with BPD on either the form discrimination [$t(58) = -0.41$, $p = 0.684$] or dot motion discrimination [$t(52) = 0.066$, $p = 0.947$] tasks. There were also no differences between these groups on static contrast sensitivity [$t(52) = 0.58$, $p = 0.567$] and a repeated measures ANOVA revealed no significant differences on moving grating contrast sensitivity tasks [$F(1,40) = 0.02$, $p = 0.88$].

Discussion

Visual processing was assessed in individuals with BPD on a set of psychophysical tasks designed to test different pathways or channels. Contrast sensitivity for static and moving gratings were used to evaluate properties relevant to the M and P pathways. These tests indicated a generalized deficit in moving grating performance across all temporal frequencies tested (2.1 Hz, 9.3 Hz, and 18.7 Hz), with intact thresholds for a static, high spatial frequency grating. Subjects with BPD also exhibited deficits in dot motion discrimination, while threshold for form discrimination was unaffected. These findings were not a function of mood state, but were found in both euthymic and ill participants. The BPD group performed similarly to HC subjects on form discrimination, possibly indicating that the ventral pathway of the cortical visual system is unimpaired in this population.

Evaluation of M and P pathway visual processing in BPD indicated a generalized deficit in moving grating performance across all temporal frequencies tested (2.1 Hz, 9.3 Hz, and 18.7 Hz). These moving contrast sensitivity findings are not due to differences in general attention to the task or cooperation, as a similar number of trials was required to reach threshold for both groups. Our findings are similar to those previously reported in schizophrenia patients (7) and may implicate similar M-mediated pathway dysfunction in BPD. Furthermore, profound deficits in backward masking have been reported in those with BPD, both during and after a manic state, and seem to appear after the initial onset of symptoms as they were not found in those at risk for developing BPD (12, 13, 43-45). These findings indicate a possible threshold model for transient pathway dysfunction in this disorder. Perris (14) reported lower flicker fusion frequencies in BPD, also possibly implicating deficits in temporal processing at higher modulation frequencies. Finally, Chen et al. (5) also reported findings consistent with a temporal processing deficit in individuals with BPD. In their velocity discrimination task, the BPD group showed impaired velocity discrimination at higher velocities, with intact slow and intermediate velocity discrimination. In the current study, participants with BPD did not show deficits on the static contrast sensitivity task, suggesting a differentiation between possibly impaired M pathway functioning and intact P pathway processing. Importantly, this does not necessarily indicate a deficit in the M neurons within the lateral geniculate nucleus. Cells sharing M tuning characteristics are also found among retina ganglion cells and in the visual cortex.

Further evaluation of moving grating performance with respect to mood state revealed that HC participants performed better than euthymic participants. However, ill participants performed intermediately, differing neither from HC subjects, nor from euthymic patients with BPD. Keri et al. (46) reported deficits on a Vernier threshold task for patients with BPD in the depressed state for both M- and P-biased conditions, but after remission the

deficits were no longer significant. In the current study, we analyzed both depressed and manic participants within the same group. Further studies to investigate this finding separately in depressed and manic participants may be able to elucidate this finding. Perhaps visual processing is preferentially affected in specific mood states; however, our sample size and cross-sectional design did not allow us to investigate this possibility. Due to the overall finding that HC subjects performed better than patients with BPD, and that the HC subjects further performed better than euthymic individuals with BPD, perhaps performance was positively affected by a particular mood state. While depressed participants have shown contrast sensitivity deficits (21, 47, 48), manic participants have not been studied, and may perhaps experience enhanced contrast sensitivity. To the extent that lower levels of dopamine are found in patients with depression, and that antidepressant medication serves to both alleviate depressive symptoms and sometimes induce mania symptoms in those with BPD, it is possible that altered state-dependent dopamine levels affect contrast sensitivity in opposing directions (47). Dopaminergic amacrine cells in the retina, for example, are sensitive to luminance contrast (49). Likewise, decreased neural excitation via glutamate, and a subsequent down regulation of GABA receptors, has been postulated to affect visual filling-in effects (50) and motion processing (51). As the current psychophysical tasks cannot address these issues, further research is needed to investigate the possible role of state-dependent neurotransmitter functioning on perception in patients with BPD.

Participants with BPD exhibited a selective deficit in dot motion discrimination, a measure that may implicate dorsal cortical pathway function, in particular the middle temporal (MT) visual region. This finding was not a function of mood state, but rather was seen in both euthymic and ill participants. Because the dot stimuli used in this task were relatively high spatial frequency stimuli presented a high contrast, this motion task could be processed by P type neurons. Neurophysiological studies indicate that dot coherence activates the cortical region MT within the dorsal pathway. This motion discrimination deficit differs from the results of Chen et al. (52), who did not report differences between the BPD group and HC subjects using similar psychophysical tasks. One possible explanation for the difference in results may be related to task properties; while Chen did include a task with the same dot density as the data reported here (100 dots), their display duration was shorter (90 msec versus the 500 msec used in our study) and they presented five predetermined motion coherence levels while our study used an individualized staircase method. Another possible explanation is that our study used a larger sample size and may therefore have greater power to detect differences in motion processing.

Neuropsychological function was tested in all participants in the study. While the BPD group exhibited impaired psychomotor speed (as assessed by the digit symbol task), this finding was dependent on mood state. Further investigation into performance with respect to mood state indicated similar performance between the euthymic BPD group and HC group, while participants endorsing depressive or manic symptoms performed significantly worse than the other groups. These findings extend previous reports of impaired performance by individuals with BPD on the digit symbol tasks (1, 53). Mahli et al. (54) also reported state related impairment on tasks of psychomotor performance, with depressed patients performing poorly compared with euthymic and manic individuals, however other studies have failed to find state-related differences in performance on the digit symbol task (1, 53).

Performance in the domain of attention (as assessed by the digit span task) followed a similar pattern. Overall, participants with BPD exhibited deficits compared to HC participants on this task of focused attention. Furthermore, the ill BPD group showed significantly impaired performance when compared with euthymic participants with BPD and with HC subjects. Previous studies employing the digit span task have failed to find an overall significant difference between HC subjects and patients with BPD, and between patients with BPD that were euthymic and experiencing a mood state (1, 54, 55).

Visual performance on contrast sensitivity gratings was correlated with degree of mania or depression, as well as with neuropsychological performance. Mania was correlated with impaired static contrast sensitivity. Interestingly, Digit Symbol performance significantly predicted measures of contrast sensitivity across diagnostic groups in regression analyses, but this was likely driven by the strong correlations found only in HC participants. Participants with BPD did not show this relationship, indicating that perhaps differences in dorsal pathway integrity lead to different levels of visual perception influence on psychomotor speed performance. Conversely, the BPD group performed similarly to the HC group on P-mediated tasks, and these were associated with a range of cognitive tasks in the BPD group but not in HC group. This difference in associations between psychophysical visual task performance and neuropsychological functioning may indicate differentially affected information processing streams in BPD. For example, in schizophrenia, Keri et al. (56) found that disrupted functionality of the M-pathway projections to frontal cortex subsequently impacted attention filters, higher order perceptual organization and natural scene processing in those with schizophrenia. Importantly, they found significant correlations between perceptual organization and M-mediated tasks in both schizophrenia and HC subjects. In the current study, the strikingly different pattern of associations between psychophysical tasks of early visual processing and neuropsychological performance may be the result of neural rewiring during acute mood episodes that may lead to both increased vulnerability to life stress and higher order cognitive dysfunction. Several reports of negative correlations between the number of mood episodes and neuropsychological performance support this theory (57, 58). In summary, these findings are consistent with reports in schizophrenia indicating that lower level visual dysfunction may impact higher order cognition in ways that are distinguishable from healthy controls (7, 30, 56). However, as the sample sizes for these analyses were low and the analyses correlational in nature, further studies are needed to investigate causal relationships between psychophysical tasks of visual processing and cognition, and to further evaluate whether a differential relationship exists between M- and P-pathway dysfunction and different types of higher order cognition in those with BPD.

There are several limitations to this study. While only 11 of our participants with BPD were not taking medication at the time of testing, three patients were prescribed lithium alone, and nine were prescribed lithium in combination with other medications at the time of testing. Lithium has been shown to affect eye tracking in those with BPD, which may differentially affect the motion compared to static tasks in this study (59, 60, 61). Furthermore, atypical antipsychotic medication was reported to normalize contrast sensitivity in schizophrenia patients while typical antipsychotics increased contrast detection thresholds (62). In the current sample, the majority of patients were prescribed atypical antipsychotics (n = 29)

compared to typical ($n = 2$) or a combination of typical and atypical ($n = 2$). To the extent that medication effects can be generalized from schizophrenia, the large number of participants prescribed atypical antipsychotics at the time of testing suggests that the contrast sensitivity deficits reported here may represent a conservative report of the visual processing deficits associated with BPD. Finally, it must be reiterated that medication status was not related to performance on any of the tasks assessed in this study. Similarly, the effect of medication on neuropsychological performance in BPD is unclear. Lithium has been reported to have negative effects on psychomotor performance and memory (63). However, other investigators have reported potentially neuroprotective effects of mood stabilizers in BPD (1, 3, 64). Studies focusing on non-medicated participants may clarify the role of medication on visual processing and neuropsychological performance. In addition, for our analyses of mood state within the BPD group, we collapsed across the manic and depressed states combining depressed ($n = 6$), manic ($n = 14$), hypomanic ($n = 7$), and mixed ($n = 5$) individuals due to the small number of subjects that were experiencing a mood state at the time of testing.

In conclusion, the current study provides new findings with respect to visual perception in BPD. This is the first study to our knowledge analyzing performance in a large sample of individuals with BPD on these tasks of visual psychophysics, and investigating the relationship between visual processing and mood state. We also have attempted to relate these new findings with the established body of literature on neuropsychological performance in BPD. While our study indicates that neuropsychological impairment in BPD may be largely state related, deficits in visual processing appear to be a trait of BPD illness and are present even during periods of euthymia. This suggests that the pathophysiology of BPD affects visual pathways along visual cortical regions, and that these deficits may be selective to perceptual processing of some motion attributes. Studies utilizing experimental manipulation of pharmacological treatment in conjunction with visual testing could determine if mood-stabilizing drugs worsen or ameliorate these deficits, and studies of relatives could indicate whether these deficits might be vulnerability markers for familial risk.

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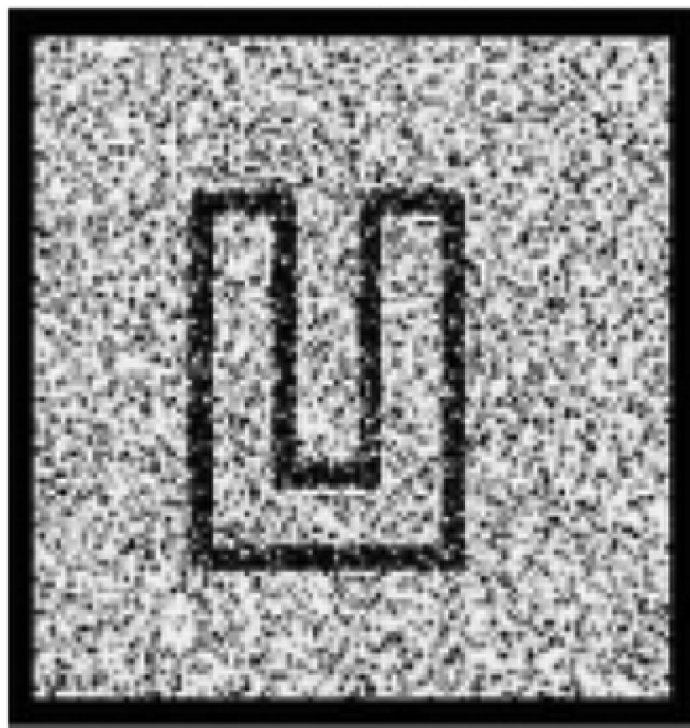
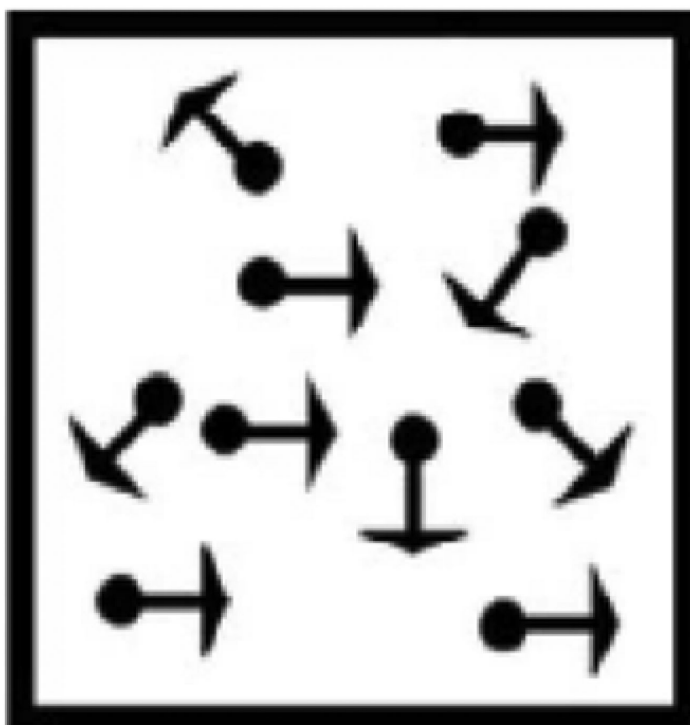
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a**b**

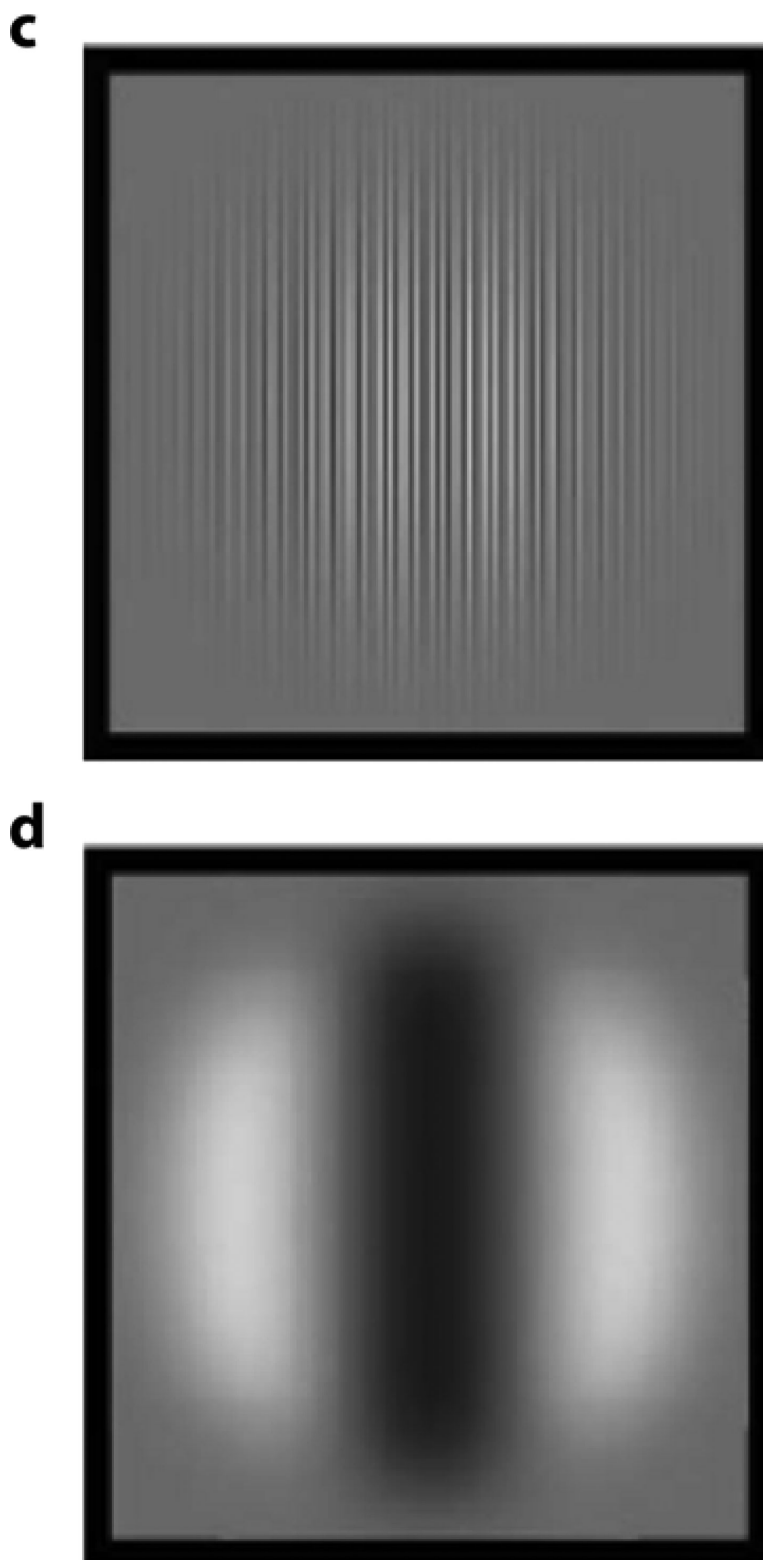


Fig. 1.

Stimuli used in psychophysical vision tests: **(A)** form stimulus; **(B)** motion stimulus (arrows represent the trajectory of each dot); **(C)** pattern detection stimulus, high spatial frequency vertical grating; and **(D)** flicker detection stimulus, low spatial frequency grating.

Table 1

Subject characteristics

Measure	Healthy controls (n = 63)	Euthymic BPD (n = 27)	Ill BPD (n = 31)
Age, years	38.87 (11.06)	42.48 (9.79)	38.69 (11.17)
Digit Span	10.32 (2.87)	9.96 (3.82)	8.55 (2.64)
Digit Symbol	10.00 (2.63)	9.19 (2.60)	7.35 (2.55)
Picture Completion	9.32 (3.56)	8.78 (3.20)	8.06 (3.43)
Similarities	8.89 (3.20)	9.22 (2.86)	8.65 (2.76)

Values are indicated as mean (standard deviation). BPD = bipolar disorder.

Table 2

Mean (standard deviation) form and dot motion discrimination values (% noise)

Measure	Healthy controls	Euthymic BPD	Ill BPD
Form	70.80 (10.10); (n = 62)	72.20 (10.60); (n = 29)	68.40 (10.70); (n = 32)
Dot motion	85.94 (7.79); (n = 60)	75.98 (20.60); (n = 27) ^a	76.08 (16.00); (n = 28) ^a

BPD = bipolar disorder; n = number of subjects.

^aHealthy controls were significantly greater than euthymic and ill subjects with BPD.

Table 3

Mean (standard deviation) contrast sensitivity for gratings (log10 contrast sensitivity)

Measure	Healthy controls	Euthymic BPD ^a	III BPD ^a
Static	1.62 (0.49); (n = 64)	1.69 (0.36); (n = 26)	1.48 (0.58); (n = 29)
2.1 Hz	2.13 (0.17); (n = 58)	2.07 (0.16); (n = 20)	2.10 (0.15); (n = 23)
9.3 Hz	2.08 (0.17); (n = 58)	1.97 (0.23); (n = 20)	2.01 (0.19); (n = 23)
18.7 Hz	1.53 (0.23); (n = 58)	1.43 (0.22); (n = 20)	1.50 (0.26); (n = 23)

BPD = bipolar disorder; n = number of subjects.

^aMarginally significant main effect of Group across tests ($p = 0.054$).

Table 4

Correlation of visual tests and symptoms of mania or depression on the YMRS and MADRS scales

	Dot motion	Form	Static	2.1 Hz	9.3 Hz	18.7 Hz
YMRS	−0.060 (n = 52)	−0.157 (n = 58)	−0.448 ^a (n = 52)	0.039 (n = 45)	0.019 (n = 46)	0.021 (n = 45)
MADRS	−0.022 (n = 53)	−0.084 (n = 59)	−0.135 (n = 53)	−0.170 (n = 45)	0.013 (n = 47)	−0.034 (n = 46)

YMRS = Young Mania Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; n = number of subjects.

^a
p < 0.01.

Table 5

Significant linear regression analyses of the relationship between neuropsychological variables and visual task performance^a

Dependent variable	Adjusted R^2 of model	β	Significant predictor	t -value	p-value
Motion discrimination	0.095	-0.322	Diagnosis	-3.51	0.001
Motion discrimination	0.198	0.231	Picture Completion	2.41	0.018
Contrast sensitivity (2.1 Hz)	0.075	0.296	Digit Symbol Coding	2.67	0.009
Contrast sensitivity (18.7 Hz)	0.058	0.282	Digit Symbol Coding	2.59	0.011

^aDiagnosis was coded 1 = healthy controls, 2 = bipolar disorder.

Table 6

Correlation of visual tests and neuropsychological performance

		Dot motion	Form	Static	2.1 Hz	9.3 Hz	18.7 Hz
Healthy controls	Digit Span	0.21 (n = 57)	0.05 (n = 59)	0.20 (n = 59)	0.03 (n = 57)	0.05 (n = 60)	-0.20 (n = 61)
	Digit Symbol	0.09 (n = 57)	0.003 (n = 59)	0.42 ^b (n = 59)	0.37 ^d (n = 57)	0.31 ^d (n = 60)	0.35 ^d (n = 61)
	Picture Completion	0.43 ^b (n = 57)	0.10 (n = 59)	0.19 (n = 59)	0.03 (n = 57)	-0.16 (n = 60)	0.20 (n = 61)
Bipolar disorder	Similarities	0.01 (n = 56)	-0.21 (n = 58)	0.22 (n = 58)	0.15 (n = 56)	0.10 (n = 59)	0.15 (n = 60)
	Digit Span	0.30 (n = 53)	0.26 (n = 59)	0.30 ^d (n = 53)	-0.03 (n = 45)	0.04 (n = 47)	0.25 (n = 46)
	Digit Symbol	0.23 (n = 53)	0.17 (n = 59)	0.001 (n = 53)	0.18 (n = 45)	0.13 (n = 47)	0.22 (n = 46)
	Picture Completion	0.31 ^d (n = 53)	0.24 (n = 59)	0.36 ^d (n = 53)	-0.03 (n = 45)	0.18 (n = 47)	0.20 (n = 46)
	Similarities	0.33 ^d (n = 53)	0.28 ^d (n = 59)	0.36 ^b (n = 53)	0.20 (n = 45)	0.13 (n = 47)	0.04 (n = 46)

n = number of subjects.

^a p < 0.05.^b p < 0.01.